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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,863	08/17/2006	Claude Dal Farra	0591-1010	9928

466 7590 03/16/2009

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ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
03/16/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,863	DAL FARRA ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-29 and 31-36* is/are pending in the application.

4a) Of the above claim(s) *28,29 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-27,31-33,35 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/17/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Election/Restriction filed on January 28, 2009 is acknowledged. Claims 1-16 and 30 have been cancelled, and new claims 31-36 have been added. Claims 17-29 and 31-36 are pending in this application.

Restriction

1. Applicant's election with traverse of Group I (claims 15-27) and the species election of SEQ ID NO:1, water as the single acceptable solvent, to reduce, eliminate or prevent excess of subcutaneous fat as the single disorder, and water-in-oil emulsions as the single formulation in the reply filed on January 28, 2009 is acknowledged. The traversal is on the ground(s) that the "determination of the lack of unity is possible only when the claims of different groups lack a "special technical feature" relative to one another. In the present case, claims 17 and 18 are generic to the compositions of the dependent claims. The compositions of claims 25, 15 and 17 of Group I are used in the method according to claims 28-30 of Group II. It is believed that the claims by definition share the same special technical feature." Applicant further argues that "Ni et al do not encompass nor read on SEQ ID NOS: 1-9 of the amended claims. Thus, Ni et al fails to disclose the peptides of the claims." In regards to species election, Applicant argues that "the elected solvent shares technical feature with other solvents because they are all chemically equivalent and safe. It is unclear why the selection of one solvent would make a patentable distinction over another...the elected vector shares technical feature with other vectors as they intend to improve penetration and bioavailability of active

ingredient in the skin…the elected disorder shares technical feature with cellulitis and orange peel as "excess of subcutaneous fat" results in unaesthetic signs called "cellulitis" and "orange peel"…the formulation "hydro-alcoholic solution" shares technical feature with "aqueous solution" as they are chemically equivalent". This is not found persuasive because Ni reference teaches the peptide of broad claim 17 of the instant claims. Claim 18 is not a genus claim, as Applicant indicates, but a species claim, which is dependent on the broad genus claim 17. The species claimed in claim 18 may be novel over the peptides disclosed in Ni reference; however, Ni reference teaches the peptides of the broad genus claim, meeting the limitation of claim 17. Therefore, the lack of unity is present, and the special technical feature of the broad genus peptide is disclosed in the Ni reference.

2. In regards to the Applicant's arguments to election of species, the species are patentably independent and distinct due to different structures, properties and mechanisms involved. For example, for different cosmetically or pharmaceutically acceptable solvents, water has the chemical formula H_2O and a boiling point of 100ºC; propylene glycol has the chemical formula $C_3H_8O_2$ and a boiling point of 188.2ºC. Further, search for one would not necessarily lead to the other. Different cosmetic or pharmaceutical vectors are patentably independent and distinct due to their different structures. For example, liposome has the structure of micelles; talc is a mineral and has the chemical formula $Mg_3Si_4O_{10}(OH)_2$. Further, search for one would not necessarily lead to the other. Different formulations are patentably independent and distinct due to the different components involved in the formulation. For example, oil

solutions would involve some type of oil solution, and powders would require a dry form of the composition. Further, search for one would not necessarily lead to the other.

The requirement is still deemed proper and is therefore made FINAL. Claims 28-29 are withdrawn from further consideration, pursuant to 37 CFR 1.142(b), as being drawn to nonelected invention, there being no allowable generic or linking claim. Claim 34 is withdrawn from further consideration as being drawn to nonelected species. A search was conducted on elected species, SEQ ID NO: 1, and this was found free of prior art. The search was extended to the other species, and these too were found free of prior art. A search extended to the broad claim 17, and a prior art was found. Claims 17-27, 31-33 and 35-36 are examined on the merits in this office action.

TRADEMARK

3. The use of the trademark M2010A LUMAC® has been noted in this application at page 15, line 8. The use of the trademark Montanov 68, Eutanol G, Phenonip, Simugel EG, Emulgade SEV, Eumulgin B2, Cetiol OE, Carbopol Ultrez 10 on pages 18-19. These should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Objection

4. Claim 17 is objected to for the following reason: Claim 17 recites an amino acid sequence $(AA)_n$-Pro-X1-X2-X1-X3-Lys-X1-Arg-X4-X5-$(AA)_n$. This sequence needs to be added to the CFR listing, according to 37 CFR 1.821-1.825. The peptide sequence is also missing the sequence identifier. The proper way to claim a peptide sequence is for example, SIINFEKL (SEQ ID NO:1) (see 37 CFR 1.821(d)). This error should be corrected.

5. Claim 26 is objected to for the following minor informality: Claim 26 recites, "…wherein said composition takes the form of a cosmetic and/or dermatological composition…" This does not read right. Applicant is advised to change this to, for example, "…wherein said composition is in a cosmetic and/or dermatological composition..." or "...wherein said composition is in the form of a cosmetic and/or dermatological composition..."

6. Claim 27 is objected to for the following minor informality: Claim 27 recites, "…said composition can take the form of an aqueous or hydro-alcoholic solution." This does not read right. Applicant is advised to change this to, for example, "...said composition is in an aqueous or hydro-alcoholic solution."

7. Claim 35 is object to for the following minor informality: Claim 35 recites, "…wherein said composition can take the form of an oil solution or emulsion…" This does not read right. Applicant is advised to change this to, for example, "...wherein said composition is in an oil solution or emulsion..."

8. Claim 36 is object to for the following minor informality: Claim 36 recites, "…wherein said composition can take the form creams, suspensions, or powders…" This does not read right. Applicant is advised to change this to, for example, "...wherein said composition is in the form of creams, suspensions, or powders..." or "wherein said compositions is selected from creams, suspensions, or powders…"

9. The specification is objected to for the following minor informality: the sequence of formula (I) on page 3 of the specification is missing the sequence identifier (see 37 CRF 1.821(d)). This error should be corrected.

10. The specification is objected to for the following minor informality: on page 8, lines 21-23, the specification discloses sequences ID N^{o} (1) to ID N^{o} (9). Amendment to the specification filed on June 4, 2007, Applicant amended sequence ID N^{o} to SEQ ID NO. To be consistent throughout the application, Applicant is advised to correct this error. Furthermore, the sequence Pro-Leu-Asp-Thr-Ala-Lys-Val-Leu-Gln disclosed on page 8, line 23 is missing the sequence identifier. This error should be corrected.

11. The specification is objected to for the following minor informality: on page 17 of the specification, Peptide ID N^{o} (1) is disclosed in PHASE D. This should be corrected to SEQ ID NO: 1. Further, on page 19, Peptide ID N^{o} (1), disclosed in PHASE D, should also be corrected to SEQ ID NO: 1. Furthermore, on page 19, Peptide ID N^{o} (1) disclosed on "3. Firming-Slimming-Anti-Cellulite Gel", Peptide ID N^{o} (1) should also be corrected to SEQ ID NO: 1.

Rejection

35 U.S.C. 112, 2nd

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 17-27, 31-33 and 35-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

14. Claim 17 recites, "…is any amino acid or derivative of said amino acid…" It is unclear what is encompassed within the derivative of said amino acid. The specification does not fully define what is meant by the term "derivative" of said amino acid. A derivative is any compound that is derived from the wild-type. According to on-line Medical Dictionary, a derivative is a chemical substance derived from another substance either directly or by modification or partial substitution (see http://cancerweb.ncl.ac.uk/omd/about.html, enclosed). Therefore, a derivative of an amino acid can be "any compound" that is derived from an amino acid or modified amino acid. It can have completely different structure. Therefore, it is unclear what is encompassed within the derivative of said amino acid.

35 U.S.C. 112, 1st

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 17-27, 31-33 and 35-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a composition comprising a protein fragment of the uncoupling protein (UCP) family, as an active ingredient, alone or in

association with at least one other active agent, wherein the protein fragment is a peptide of formula $(AA)_n$-Pro-X1-X2-X1-X3-Lys-X1-Arg-X4-X5-$(AA)_n$…(AA) is any amino acid or derivative of said amino acid. The generic statements active agent and derivative of said amino acid do not provide ample written description for the compounds since the claims do not describe a single structural feature. The specification does not clearly define or provide examples of what qualify as compounds of the claimed invention.

As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable claim 17 is broad generics with respect all possible compounds encompassed by the claims. The possible structural variations are limitless to any class of peptide or a peptide-like molecule, any small molecules, any class of polymers, any class of organic molecules that function as active agents. It must not be forgotten that the MPEP states that if a peptide is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of derivatives. The specification is void

of organic molecules, small molecules that functions as a peptide-like molecule and other therapeutic agents that qualify for the functional characteristics claimed as an active agent and derivative of an amino acid.

The specification discloses that "the invention relates to the use of proteins of the UCP family or peptide fragments of the UCP family or biologically active derivatives, as a slimming active agent, in or for the preparation of a dermatological and/or cosmetic composition" (see paragraph [0012] of instant specification US 2008/0171076 A1). Further, the specification discloses that "current preferred method of embodiment of the invention, the slimming active agent is the peptide having the sequence ID NO: 1" (see paragraph [0038] of instant specification US 2008/0171076 A1). The specification discloses that "to the composition of the invention, other active agents intended among other things for the treatment of cellulite and the orange peel skin phenomenon can be added…an active promoting lipolysis (see paragraph [0059] of instant specification US 2008/0171076 A1). The specification discloses that "on a therapeutic level, only the use of active ingredients capable of acting on protein expression have been considered. Thus, patents JP2003113104 and JP2003113106 describe, for example, compositions made from plant extracts that are able to stimulate UCP protein expression in brown tissue adipocytes (see paragraph [0008] of instant specification US 2008/0171076 A1). The specification describes "the active ingredient makes it possible to prevent the appearance of cellulite as well as to fight against its aggravation" (see paragraph [0044] of instant specification US 2008/0171076 A1). The specification is limited to the peptide of UCP family and SEQ ID NOS: 1-9. The working example describes Montanov 68,

squalane, DUP IPP, Eutanol G, Phenonip (Phase A), Demineralized water, Glycerine, Butylene Glycol (Phase B), SImugel EG (Phase C), and Peptide ID NO: 1, Perfume, colorant (Phase D) (see Example 2); Carbopol Ultrez 10, Demineralized water, DUB DIOL, EDTA, Glydant Plus Liquid, Peptide ID NO:1, TEA, Perfume, and water-soluble colorant (see paragraph [0105] of instant specification US 2008/0171076 A1). The working example only describes SEQ ID NO: 1, as the active agent. Other ingredients included in the working example does not appear to be active agents for slimming purposes, but carriers. For example, CARBOPOL® ULTREZ 10 is self wetting crosslinked polyacrylic acid polymer that provides greater versatility in formulating (see http://www.homecare.noveon.com/products/carbopol/ultrez_10.asp). The specification does not describe any other active agent, such as synthetic polymers comprising repeating polypeptide units or any other proteins in plants, vegetables and meat, or any other type of peptide or peptide-like molecule that act as active agent for slimming purposes. In regards to derivative of amino acid, the specification discloses that “the peptide is or is not in a protected form…the amino acid derivatives and the peptide derivatives also relate to amino acids and peptides bound together by a pseudo-peptide bond” (see paragraph [0031] of instant specification US 2008/0171076 A1). The specification further discloses that the peptide can be in L, D, or DL-configuration (see paragraph [0032] of instant specification US 2008/0171076 A1). Descriptions of SEQ ID NOS: 1-9 and ingredients such as CARBOPOL® ULTREZ 10 (for example) are not sufficient to encompass numerous other proteins, small molecules, organic compounds, polymers and other molecules that belong to the same genus, active agents.

Descriptions of peptide being in or not in a protected form, bound together by a pseudo-peptide bond, and in L, D, or DL-configuration are not sufficient to encompass numerous other compounds or molecules that belong to the same genus, derivatives of amino acid. For example, there are varying lengths, varying amino acid compositions, varying compositions, and numerous distinct qualities that make up the genus. For example, for proteins, there are 20 naturally occurring amino acids. A peptide derivative of SEQ ID NO: 1 for example, would have $10^{20} = 1 \times 10^{20}$ different possibilities. When additions, deletions and other modifications (non-natural amino acids, for example) are factored into the equation, the possibility is vast. For derivatives of amino acids, any compound or molecule derived or modified from the wild-type amino acid would be a derivative of an amino acid. This implies that a structure that does not relate to a wild-type amino acid could be a derivative of an amino acid, as long as it was derived from the amino acid. There is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed.

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate"). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

17. Claims 17-18, 20-27, 31-33 and 35-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO: 1, does not reasonably provide enablement for SEQ ID NOS: 2-9. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature or the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (5) the breadth of the claims:

The claims are drawn to a composition comprising a protein fragment of the uncoupling protein (UCP) family, as an active ingredient, alone or in association with at least one other active agent, wherein the protein fragment is a peptide of the formula $(AA)_n$-Pro-X1-X2-X1-X3-Lys-X1-Arg-X4-X5-$(AA)_n$, wherein (AA) is any amino acid or derivative of said amino acid, and SEQ ID NOS: 1-9.

(2) The state of the prior art and (4) the predictability or unpredictability of the art:

With regards to the effect of amino acid substitution in a peptide or protein, the art is unpredictable.

Rudinger (Peptide Hormones, JA Parsons, Ed., 1976, 1-7) teaches that, "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori but must be determined from case to case by painstaking experimental study" (see p. 6). Additionally, SIGMA states that with regards to design of peptide sequences that, "Even for relatively short sequences, there are essential and non-essential (or less important) amino acid residues, although the relative importance of the individual amino acid residues is not always easy to determine" (see p. 1). SIGMA further describes what effect some substitutions may have, rather than what effect they will have on hydrophobicity, secondary structure (which will affect tertiary and quaternary structure), and solubility. Additionally, Schinzel et al (FEBS, 1991, 286(1, 2): 125-128) teach that the substitution of Lys^{539} by an

arginine caused a 600 fold reduction, substitution of Arg^{534} by a glutamine caused an even larger 7000-fold reduction of the catalytic rate while substrate binding remained essentially unaffected. The reference teaches that Arg^{534} to Gln exchange reduces the catalytic rate near to inactivity and even the conservative Lys^{534} to Arg exchange caused marked decrease of activity (see abstract).

With regards to prediction of the native conformation of a protein (structure), the art is unpredictable. Berendsen (Science, 1998, 282: 642-643) states, "The prediction of the native conformation of a protein of known amino acid sequence is one of the great open questions in molecular biology and one of the most demanding challenges in the new field of bioinformatics" (see p. 642). Furthermore, Berendsen states that "Folding to the stable native state [computationally] has not (yet) occurred, and the simulations do not contain any relevant statistics on the process. The real protein will fold and refold hundreds to thousands of times until it stumbles into the stable conformation with the lowest free energy. Because this hasn't happened (and couldn't happen) in the simulations, we still cannot be sure of the full adequacy of the force field" (see p. 642).

Further, the effects of a single amino acid substitution can have substantial effects on proteins in structure and/or function and are exemplified by the difference between hemoglobin (Hb) and abnormal hemoglobins, such as sickle-cell hemoglobin (HbS). Voet et al teaches that the mutant hemoglobin HbE [GluB8(26)β to Lys] has, "no clinical manifestations in either heterozygotes or homozygotes" (see p. 235). Further, Hb Boston and Hb Milwaukee both have single point mutations which results in altered binding affinity and ineffective transfer from the Fe(III) to Fe(II) oxidation state.

Conversely, a single point mutation in Hb Yakima results in increased oxygen binding by the heme core, and in Hb Kansas, the mutation causes the heme center to remain in the T state upon binding oxygen (rather than structurally rearranging to the R state) (see p. 236). Further, HbS is a single point mutation, Val to GluA3(6)β (see p. 236), which results in deformation and rigidity of the red blood cell. The mutation also provides protection against most malarial strains.

Additionally, the art recognizes that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori but must be determined from case to case by painstaking experimental study". Additionally, SIGMA states that with regards to design of peptide sequences that, "Even for relatively short sequences, there are essential and non-essential (or less important) amino acid residues, although the relative importance of the individual amino acid residues is not always easy to determine" (see p. 1). SIGMA further describes what effect some substitutions may have, rather than what effect they will have on hydrophobicity, secondary structure (which will affect tertiary and quaternary structure), and solubility. Therefore, any modification on the polypeptide might have an affect on the polypeptide, thus vast numbers of experimentation would be required to see if the polypeptide modified with the oxime-containing non-natural amino acid would have the same affect on certain diseases as the wild-type polypeptide. As with all peptides, activity is based on the structure of the peptide. That is, the peptide has to have the proper structure to recognize the specific receptor for the peptide to be active. The sate of the art for prediction of the native conformation of the protein is, at best, a vague science. For

example, in peptide chemistry, Ngo et al teach that for protein and peptides, a "'Direct' approach to structure prediction, that of directly simulating the folding process, is not yet possible because contemporary hardware falls eight to nine orders of magnitude short of the task" (see p. 493). Accordingly, it is not known if an efficient algorithm for predicting the structure exists for a protein or peptide from its amino acid alone (see p. 492). Thus, activity of a given peptide cannot be based on its structure alone. Similarly, the Rudinger article (see the conclusion in particular) states "The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from the case to case by painstaking experimental study." Finally, in an article published in Science, the author concluded that "one of the 'grand challenges' of high-performance computing-predicting the structure of proteins-acquires much of the flavor of the Holy Grail-quest of the legendary knights of King Arthur. It is extremely desirable to possess but extremely elusive to obtain" (see p. 643 in Berendsen). Berendsen et al states "at the present level of sophistication, [homology modeling] are effective for only 25% of the proteins for which the amino acid sequence is known" (see p. 642). It is known that proteins fold into their native conformation spontaneously and within seconds. The underlying principle of folding is known in the art yet the art lacks the ability to mimic native folding process (see p. 642 in Berendsen). "[E]xisting computers cannot sample enough configurations in a reasonable time to come up with the thermodynamically stable native structure;…we are not too sure that the available force field descriptions, which we need to compute the energy of a each configuration, are accurate enough to come up with

reliable free energy of a conformation" (see p. 642 in Berendsen). Berendsen et al discloses the principle of the "Levinthal's paradox" which states that if one was to assume that "three possible states for every flexible dihedral angle in the backbone of a 100 protein residue, the number of possible backbone configuration is 3^{200}. Even an incredibly fast computational or physical sample in 10^{-15}s would mean that complete sample would take 10^{80}s, which excides that age of the universe by more than 60 orders of magnitude." Other tools such as lattice models provide insight into principle of folding, but to provide no solutions to the real folding problems (see p. 643 in Berendsen). The art has recognized that even single point mutations can cause diverse effects on peptide activity. It has been shown in numerous peptides that a single amino acid can have deleterious effects on the peptide. For example, Bradley et al teach that a single substitution of Ala to Gly in six analogous structural peptides of an ankyrin protein resulted in dramatic and diverse effects on protein stability (see Bradley et al). Sickle cell anemia can be traced to a single point mutation at position six in the beta globulin protein. The instant application claims are open to oxime modification at any position of any therapeutic polypeptides. The working examples given do not sufficiently establish whether any peptide encompassed by the claimed invention would behave similarly. Given that point mutations can lead to abolishment of activity, one would be burdened with undue experimentation to screen the numerous compounds in attempting to find those that have the same activity as the wild-type therapeutic polypeptides.

Given that one could not determine the structure of a protein computationally, and that the effect of amino acid substitution is unpredictable, it flows logically that one

would be unduly burdened with experimentation to determine the effect of amino acid substitution(s) in a peptide or protein, with regards to structure, function, or physical/chemical properties. Therefore, making any peptide fragment having 10 amino acid residues that has the same activity as the claimed protein, one would be unduly burdened with experimentation to determine the effect of amino acid content, substitution(s), addition and deletions in a peptide or protein, with regards to structure, function, or physical/chemical properties.

(3) The relative skill of those in the art:

The relative skill of those in the art is high.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples:

The specification discloses that the invention relates to the use of proteins of the UCP family or peptide fragments of the UCP family or biologically active derivatives as a slimming active agent, for the preparation of a dermatological and/or cosmetic composition (see paragraph [0012] of instant specification US 2008/0171076 A1). The specification discloses SEQ ID NOS: 1-9 that belong to the UCP family (see paragraph [0021] of instant specification US 2008/0171076 A1). The specification discloses that the preferred peptide fragment is SEQ ID NO: 1 (see paragraph [0022] of instant specification US 2008/0171076 A1). SEQ ID NO: 1 is PLDTAKVRLQ; SEQ ID NO: 2 is PTEVAKVRFQ; SEQ ID NO: 3 is PTDVAKVRLQ; SEQ ID NO: 4 is PTEVAKVRLQ;

SEQ ID NO: 5 is PTDVAKVRFQ; SEQ ID NO: 6 is PVDVVKTRYM; SEQ ID NO: 7 is PVDVVKTRYM; SEQ ID NO: 8 is PVDVVKTRFM; SEQ ID NO: 9 is PVDVVKTRYI. SEQ ID NOS 1 and 2 have 60% homology; SEQ ID NOS: 1 and 3 have 80% homology; SEQ ID NOS: 1 and 4 have 70% homology: SEQ ID NOS: 1 and 5 have 70% homology: SEQ ID NOS: 1 and 6 have 40% homology; SEQ ID NOS: 1 and 7 have 40% homology; SEQ ID NOS: 1 and 8 have 40% homology; SEQ ID NOS: 1 and 9 have 40% homology. The working example describes the solution containing the peptide of SEQ ID NO: 1 (see Example 1, paragraphs [0065]-[0094] of instant specification US 2008/0171076 A1). The specification discloses that SEQ ID NO: 1 is a representative of the peptide family according to the invention. Example 2 describes different composition preparations, and PHASE D contains Peptide sequence of SEQ ID NO: 1. However, there are no examples of SEQ ID NOS: 2-9. As indicated above, SEQ ID NO: 1 and 2 have a 60% homology. SEQ ID NO: 1 and 9 have 40% homology. These amino acid substitutions are not conservative substitutions. As indicated by the prior arts above, even conservative substitutions can cause decrease in protein/peptide activity. For example, Schinzel et al (FEBS, 1991, 286(1, 2): 125-128) teach that the substitution of Lys^{539} by an arginine caused a 600 fold reduction, substitution of Arg^{534} by a glutamine caused an even larger 7000-fold reduction of the catalytic rate while substrate binding remained essentially unaffected. Rudinger article (see the conclusion in particular) states “The significance of particular amino acids or sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from the case to case by painstaking experimental study.” Finally, in an article published in Science, the author

concluded that “one of the ‘grand challenges’ of high-performance computing-predicting the structure of proteins-acquires much of the flavor of the Holy Grail-quest of the legendary knights of King Arthur. It is extremely desirable to possess but extremely elusive to obtain" (see p. 643 in Berendsen). The specification does not disclose how to use the active agent, and if these SEQ ID NOS: 2-9 are as active as SEQ ID NO: 1 and work to treat excess subcutaneous fat. There is not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed. Since there are 20 naturally occurring amino acids, the possibilities are limitless.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the reference above and the high unpredictability and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to make a composition comprising a peptide fragment having activities for treating excess subcutaneous fat.

Given that one could not determine the structure of a protein computationally, and that the effect of amino acid substitution is unpredictable, it flows logically that one would be unduly burdened with experimentation to determine the effect of amino acid substitution(s) in a peptide or protein, with regards to structure, function, or physical/chemical properties. Therefore, making any composition comprising peptide fragment of 10 amino acid residues that has the same activity as the claimed protein, one would be unduly burdened with experimentation to determine the effect of amino

acid content, substitution(s), addition and deletions in a peptide or protein, with regards to structure, function, or physical/chemical properties.

35 U.S.C. 101

18. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

19. Claims 17-27, 31-33 and 35-36 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 17 recites a composition comprising a protein fragment of the uncoupling protein (UCP) family, as an active ingredient. The instant specification discloses that a composition contains proteins of the UCP family, or polypeptide or peptic protein UCP fragments, as an active agent (see paragraph [0002] of US 2008/0171076 A1). The composition comprises at least one protein of the UCP family, peptide or polypeptide fragments, or biologically active derivatives (see paragraph [0037] of US 2008/0171076 A1). Furthermore, the specification discloses that the term peptide refers to a natural or synthetic peptide (see paragraph [0029] of US 2008/0171076 A1). Ni et al (US 2003/0036646 A1) teach the peptides of human UCP proteins, indicating that this is naturally occurring protein. In the broadest reasonable interpretation of the claim, this implies that the composition includes cells that comprise the protein fragments. These proteins are naturally occurring proteins that are found in cells, and can go through natural cleavage, resulting in protein/peptide fragments. Therefore, these proteins and protein fragments are

natural phenomenon, purification or isolation of some sort is necessary. Therefore, the instant claims are directed to non-statutory subject matter.

35 U.S.C. 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

21. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Ni et al (US 2003/0036646 A1).

22. Ni et al teach human uncoupling polypeptides (see abstract). Ni reference teaches isolated UCP fragment peptides, PLDVVKVRLQ (see SEQ ID NO: 38) and PLEVVKTRLQ (see SEQ ID NO: 45) that meet the limitation of instant claim 17. Furthermore, the reference teaches that the polypeptide can be used in treatment of many different diseases, including cellulitis (see paragraph [0701]). Therefore, the reference anticipates instant claim 17.

Conclusion

23. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Julie Ha/
Examiner, Art Unit 1654